REMARKS

Claims 1-20 were previously pending in this application, and stand rejected under 35 USC § 103. This paper comprises no amendments to the claims or the specification.

Reconsideration of the application in view of the remarks provided in this paper is respectfully requested.

Rejection of claims 1-15

The claims relate to treatment of cancer using glufosfamide and gemcitabine in combination. The claims stand rejected under 35 USC § 103(a) as being unpatentable over four publications: Noble et al. (Drugs 54:447, 1997) in view of Briasoulis et al. (Eur. J. Cancer, 39:2334, 2003), Kozuch et al. (The Oncologist 6:488:2001), and Giaconne et al. (Eur. J. Cancer, 40:667, 2004).

The Office Action states that the Noble reference teaches gemcitabine was effective in treating advanced pancreatic cancer, and suggests that combinations of gemcitabine and other cancer drugs should be tested in the future. Kozuch et al. is cited as teaching the efficacy of doublet combinations of gemcitabine, ironotecan, cisplatin and 5-fluorouracil. Briasoulis is cited for teaching that glufosfamide has modest activity against advanced or metastatic pancreatic cancer (Office Action, page 3). Giaconne is cited for teaching the administration of glufosfamide as a second-line treatment of non-small-cell lung cancer. The Office Action states that both gemcitabine and glufosfamide have been successful agents for treating cancer, and that the art teaches combinations of gemcitabine with ifosfamide and other drugs. Accordingly, the reasoning goes, one of ordinary skill in the art would be motivated to administer the claimed combination. The references are further cited for suggesting certain dosages and infusion protocols.

Applicant disagrees with the rejection. The Kozuch reference teaches treatment methods using four different drugs simultaneously: namely, gemcitabine, cisplatin, 5-fluorouracyl leucovorin and irinotecan. There is no indication in Kozuch which of the four-drugs could be substituted without decreasing the effect of the combination as a whole. The Office Action does not adequately explain why someone would be motivated *a priori* to select just one of the four drugs (gemcitabine), leave out the

other three, but then substitute a second drug (glufosfamide) which the other references teach should be used as a monotherapy.

Furthermore, someone skilled in the art at the time this invention was made would not have a reasonable expectation of success based on the cited references alone. If two drugs are "equivalents", as indicated in the Office Action (page 9), then there would be no reason to suspect that the two drugs together would be any better than either drug alone. Someone skilled in the art would expect that the tissue distribution of glufosfamide would be different from ifosfamide, because of the distribution of cell-surface glucose receptors.

Proven clinical efficacy

The inventors have discovered a combination of two particular cancer drugs amongst the myriad of possible combinations that has an unexpected degree of synergy.

Prompted by data in animal models such as presented in Example 2 of this application, clinical trials were conducted to continue the investigation of the effect of the two drugs together. The unexpected synergy of gemcitabine and glufosfamide can be seen by comparing the results of this study with the clinical history of the two drugs separately. Table 1 compares results of clinical trials reported in the following publications:

A. HA Burris et al., J Clin Oncol. 15:2403-2413, 1997. "Improvements in Survival and Clinical Benefit with Gemcitabine as First-Line Therapy for Patients With Advanced Pancreas Cancer: A Randomized Trial."
B. Tarceva® (erlotinib) Full Prescribing Information. Genentech USA, Inc.
C. E Briasoulis et al., Eur. J. Cancer 39:2334-2340, 2003 (cited in the Office Action)
D. EG Chiorean, GT Tidmarsh et al., Am. J. Clin. Oncol. 33:111-116, 2010. "A phase 2 trial of glufosfamide in combination with gemcitabine in chemotherapy-naive pancreatic adenocarcinoma."

Item A was included in the Information Disclosure Statement filed October 17, 2007. Copies of items B and D are being provided in an IDS filed concurrently with this response.

TABLE 1: Clinical Efficacy of Gemcitabine and Glufosfamide

Study	Treatment	No. of Patients	Response Rate (%)	Median survival (months)	One-year Survival (%)
A	Gemcitabine alone	63	5.4	5.6	18
	5-fluorouracil alone	63	0	4.4	2
B	Gemcitabine alone	260	7.9	6.0	19.4
	Gemcitabine + Erlotinib	261	8.6	6.4	23.8
C	Glufosfamide alone	34	5.9	5.3	(not reported)
D	Gemcitabine + Glufosfamide	28	**18**	6.0	**32**

When tested alone, neither gemcitabine nor glufosfamide had a response rate better than about 8%. The combination of gemcitabine (Gemzar®) and erlotinib (Tarceva®) had a response rate of about 9%. However, the response rate of gemcitabine and glufosfamide doubled the response rate to 18%. The one-year survival in patients treated with gemcitabine or glufosfamide alone as only about 18-19%, while the one-year survival in patients treated with the two drugs together was 32%.

Greater than expected results are evidence of nonobviousness. MPEP § 716.02(a). Claims 2-15 are patentable over the cited references *inter alia* because they depend from and incorporate the features of claim 1.

Withdrawal of this rejection is respectfully requested.

Rejection of claims 16-20

These claims stand rejected under 35 USC § 103(a) as being unpatentable over a combination of the publications by Briasoulis et al. (Eur. J. Cancer, 39:2334, 2003) and Giaconne et al. (Eur. J. Cancer, 40:667, 2004) that are referred to above.

According to the Office Action, Briasoulis teaches various dosing regimens for glufosfamide, that glufosfamide has modest activity against advanced or metastatic pancreatic cancer, and that the response rate and duration of survival are comparable with gemcitabine. The Giaconne reference is cited as teaching that glufosfamide can be used as a second-line treatment for advanced non-small cell lung cancer (NSCLC). Since glufosfamide has been used as a first-line therapy for pancreatic cancer and as a second-line therapy for another cancer, the Office Action concludes that a person having ordinary skill in the art would have been motivated to administer glufosfamide to a person having chemotherapy-refractory pancreatic cancer. The Office Action does not comment on whether there would have been a reasonable expectation of success for this therapy.

Applicant disagrees with the rejection. Claims 16-20 explicitly specify treatment of pancreatic cancer. In view of the large number of approved and experimental cancer drugs referred to above, a clinician treating someone with pancreatic cancer would have several hundred possible monotherapies to choose from as second-line treatment of pancreatic cancer, and an even larger number of possible drug combinations. The Kozuch reference cited against 1-15 is also relevant here. The authors conclude that the "use of a fifth new drug added to four upfront drugs as well as use of a prolonged infusion schedule were associated with partial reversal of drug resistance." Page 493, ¶ 2. This guides the reader towards using complex drug formulations in overcoming drug resistant cancer.

With regards to the expectation of success, the Giaconne reference actually teaches against using glufosfamide for second-line cancer therapy.

> Although ifosfamide has shown important activity in first-line therapy in advanced NSCLC, in a randomized study by Fossella and colleagues . . . the response rate was lower than 1%. Glufosfamide might provide some advantages to ifosfamide treatment, but the results of our present study *do not support further investigation of its use as a second-line treatment* for NSCLC. [page 671, ¶ 2, italics added]

Proven clinical efficacy

The makers of this invention have discovered that glufosfamide is effective as a second-line therapy of pancreatic cancer in patients that have failed first-line treatment with gemcitabine. Rather than adding the glufosfamide as an adjunct to the first-line therapeutic, glufosfamide was given as a monotherapy after gemcitabine was withdrawn.

Clinical results shown in Table 2 are taken from TE Ciuleanu, GT Tidmarsh et al., Eur J Cancer.45:1589-1596, 2009: "A randomized Phase III trial of glufosfamide compared with best supportive care in metastatic pancreatic adenocarcinoma previously treated with gemcitabine." A copy of this publication is provided in an IDS filed concurrently with this response..

TABLE 2: Clinical Efficacy of Glufosfamide in Patients Previously Treated with Gemcitabine

Patient Group	Treatment	No. of Patients	Median survival (months)
All Patients	Best supportive care (BSC)	155	2.8
	Glufosfamide	148	3.4
No Insulin Use Subgroup	Best supportive care (BSC)	123	2.8
	Glufosfamide	123	3.8
Glucose Lowering Agent Use Subgroup	Best supportive care (BSC)	14	2.4
	Glufosfamide	7	**13.7**

Patients were admitted to this study if they had pancreatic cancer that had failed tor respond to gemcitabine. Overall survival was 18% higher in the glufosfamide treated group compared with the BSC control group (TE Ciuleanu et al., abstract). Median survival was increased by 3 weeks, VAS pain symptoms and CA 19-9 responses improved. For the group as a whole, the results were not statistically

significant, given the size of the study. However, the trend towards longer survival is promising, in view of the dire prognosis for pancreatic cancer — particularly cancer that was resistant to gemcitabine, the treatment of choice for pancreatic cancer at the time this inventor was made. Since glufosfamide had failed as a second-line therapy for NSCLC, it could not have been expected that glufosfamide would provide a measurable benefit for pancreatic cancer that had proved resistant to gemcitabine.

Results were even more promising in the subgroup of patients undergoing glucose modifying therapy. Non-insulin dependent diabetics on glucose lowering agents experienced an improvement in median survival of 13.7 months compared with 2.4 months in the control arm. When pancreatic cancer patients taking insulin were excluded from the analysis, a statistically significant increase in survival time was also noted in the other subgroup.

Given the rapid and ultimately fatal progression of pancreatic cancer, and the modest efficacy of currently approved treatments, it is clear that the claimed invention provides an important new modality for the management of this deadly disease.

Withdrawal of all rejections under § 103 is respectfully requested.

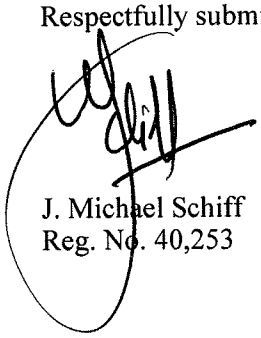
Request for Interview

Applicant requests that all rejections of this application be withdrawn, and that a Notice of Allowance be provided forthwith.

Should the Examiner identify any issues not fully resolved by the amendments and remarks presented here, he is invited to telephone the undersigned at the number indicated below.

Accompanying this Response is payment for the requisite extension of time. The Commissioner is hereby authorized to charge any additional fees or credit any overpayment in connection with this Response and the accompanying documents to Deposit Account No. 20-1430.

Respectfully submitted,



J. Michael Schiff
Reg. No. 40,253

KILPATRICK TOWNSEND & STOCKTON LLP
Two Embarcadero Center, Eighth Floor
San Francisco, California 94111-3834
Tel: 650-324-6340 Fax: 415-576-0300

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